PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

**(PCT Article 36 and Rule 70)**

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 035394-0247 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/US03/36120 | 13 November 2003 (13.11.2003) | 14 November 2004 (14.11.2004) |

International Patent Classification (IPC) or national classification and IPC

IPC(7): A23J 1/00; C07K 1/00,14/00,16/00,17/00; C12M 1/34,3/00; C12Q 1/00; G01N 33/48,33/53,33/543,33/567 and US Cl.: 422/50; 435/4,7.1,7.2,7.21,7.24,7.92,287.1,287.7,288.7; 436/514,518,541,63,824,173; 530/412,413

Applicant

CIPHERGEN BIOSYSTEMS, INC.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 14 June 2004 (14.06.2004) | 02 March 2005 (02.03.2005) |
| Name and mailing address of the IPEA/US<br>Mail Stop PCT, Attn: IPEA/ US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Leon Y Lum<br>Telephone No. 571-272-1600 |

Form PCT/IPEA/409 (cover sheet)(July 1998)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/36120

## I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-34 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 35-40, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-6, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 32-44

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 32-44

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. STATEMENT

| | | |
|---|---|---|
| Novelty (N) | Claims NONE | YES |
| | Claims 1-3,15-17 and 31 | NO |
| Inventive Step (IS) | Claims NONE | YES |
| | Claims 1-31 | NO |
| Industrial Applicability (IA) | Claims 1-31 | YES |
| | Claims NONE | NO |

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 5 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: The instant claim is repeated.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

**V. 2. Citations and Explanations:**

Claims 1-3, 15-18, and 31 lack novelty under PCT Article 33(2) as being anticipated by Hitomi et al (US 5,976,832), in light of Ilg et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150).

Hitomi et al reference teaches a diagnostic assay kit and method for detecting the presence of at least one biomarker indicative of intra-amniotic inflammation in a sample of amniotic fluid, comprising the steps of mixing an adsorbent that binds at least one biomarker associated with intra-amniotic inflammation with a sample of amniotic fluid and then monitoring said mixture for binding between said biomarker and said adsorbent, and instructions for said steps (claims 1 and 16), wherein the adsorbent is an antibody immobilized on a solid substrate (claims 2 and 17), wherein the diagnostic assay is an ELISA (claims 3 and 18), wherein said calgranulin is calgranulin C (claims 15 and 31), by disclosing assay of CAAF1 in amniotic fluid on an ELISA plate for the diagnosis of inflammatory disease (column 21, line 55 to column 22, line 58, especially column 21, lines 56-61 and column 22, lines 45-58), wherein CAAF1 is calgranulin C, as disclosed by Ilg et al reference (page 146, 2nd full paragraph, line 7 and notation 4).

Claims 4-5 and 19-21 lack an inventive step under PCT Article 33(3) as being obvious over Hitomi et al (US 5,976,832), in light of Ilg et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150), and in view of Krone et al (Analytical Biochemistry, 1997, 244:124-132).

Hitomi et al reference has been disclosed above, but fails to teach that the solid substrate is a probe, wherein said biomarker is detected by laser desorption/ionization mass spectrometry, and wherein said adsorbent is immobilized on a probe.

Krone et al reference discloses a BIAcore CM5 biosensor chip covalently derivatized with an antibody, wherein species detected during surface plasmon resonance (SPR) for biomolecular interaction analysis (BIA) is interfaced with MALDI mass spectrometry, in order to determine and distinguish between binding of multiple ligands by identifying species detected during SPR-based BIA (page 125, right column, 1st full paragraph to page 126, left column, 1st full paragraph).

It would have been obvious to one of ordinary skill at the time of the invention to modify the kit and method of Hitomi et al with a BIAcore CM5 biosensor chip covalently derivatized with an antibody, wherein species detected during surface plasmon resonance (SPR) for biomolecular interaction analysis (BIA) is interfaced with MALDI mass spectrometry, as taught by Krone et al, in order to determine and distinguish between binding of multiple ligands by identifying species detected during SPR-based BIA. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in immobilizing antibodies onto a BIAcore biosensor chip and using mass spectrometry, as taught by Krone et al, in the kit and method of Hitomi et al, since Hitomi et al teach the detection of antigens using antibody assays, and the BIAcore biosensor chip and mass spectrometry taught by Krone et al is one example of an antibody-antigen binding assay to detection antigens in a sample.

Claims 6-7 and 22-23 lack an inventive step under under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and in further view of Keene (US 5,541,291).

Hitomi et al and Krone et al references have been disclosed above, but fail to teach that said adsorbent is a hydrophobic adsorbent on a probe.

Keene reference teaches ELISA assays with surface functionalizing using hydrophobic amino acids, in order to allow

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

attachment by hydrophobic bonding to plastic surfaces (column 9, line 65 to column 10, line 9).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit and method of Hitomi et al and Krone et al, with ELISA assays with surface functionalizing using hydrophobic amino acids, as taught by Keene, in order to allow attachment by hydrophobic bonding to plastic surfaces. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in using hydrophobic amino acids to functionalize a plastic surface for ELISA assays, as taught by Keene, in the kit and method of Hitomi et al and Krone et al, since Hitomi et al and Krone et al teach ELISA assays, and a plastic surface is one type of substrate in which to perform an ELISA assay.

Claims 8-13 and 24-29 lack an inventive step under PCT Article 33(3) as being obvious over Hitomi et al (US 5,976,832), in light of Ilg et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150), and in view of Heine et al (US 6,174,664 B1).

Hitomi et al reference has been disclosed above, but fails to teach that the assay additionally tests for the presence of at least one defensin in said sample of amniotic fluid (claims 8, 10, 12, 24 26, and 28), wherein said defensin is HNP-1 (claims 9, 11, 13, 25, 27, and 29).

Heine et al reference discloses that monoclonal antibodies to the defensins HNP1-3 can be prepared for an ELISA in 96-well plates in order to screen a pregnant patient for the presence of an intraamniotic infection using amniotic fluid (column 6, lines 47-67 and column 7, lines 1-52).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit and method of Hitomi et al, with monoclonal antibodies to the defensins HNP1-3 that can be prepared for an ELISA in 96-well plates, as taught by Heine et al, in order to screen a pregnant patient for the presence of an intraamniotic infection using amniotic fluid. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in performing an ELISA on multiple antigens, as taught by Heine et al, in the kit and method of Hitomi et al, since Hitomi et al teach an ELISA kit and method using antibodies, and the 96-well plate taught by Heine et al is used for ELISA assays and can accommodate distinguishable binding assays between each of HNP-1 and calgranulin, and their respective antibodies in separate wells.

Claims 14 and 30 lack an inventive step under PCT Article 33(3) as being obvious over Hitomi et al (US 5,976,832), in light of Ilg et al (Biochemical and Biophysical Research Communications, 1996, 225:146-150), and in view of Vogl et al (The Journal of Biological Chemistry, 1999, 274(36):25291-25296) and Passey et al (The Journal of Immunology, 1999, 163:2209-2216).

Hitomi et al reference has been disclosed above, but fails to teach that said calgranlulin in the diagnostic assay is calgranulin A.

Vogl et al reference and Passey et al reference disclose binding of monoclonal antibodies to MRP8, in order to locate MRP8, which is an important regulator of cytoskeletal/membrane interactions during phagocyte activation (Vogl et al: page 25291, right column, 1st full paragraph; and page 25292, left column, 4th full paragraph), and which is a known regulator of inflammation that is expressed at the critical time and place where infiltration of the embryo by maternal cells must be regulated, wherein MRP8 is also known as S100A8 and calgranulin A (Passey et al: page 2209, left column, 1st paragraph, lines 11-13; and page 2215, 2nd full paragraph, lines 34-37).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the kit and method of Hitomi et al reference with binding of monoclonal antibodies to MRP8, in order to locate MRP8, which is an important regulator of cytoskeletal/membrane interactions during phagocyte activation, as taught by Vogl et al and Passey et al, and which is a known regulator of inflammation that is expressed at the critical time and place where infiltration of the embryo by maternal cells must be regulated, wherein MRP8 is also known as S100A8 and calgranulin A. One of ordinary skill in the art at the time of the invention would have reasonable expectation of success in performing an assay on calgranulin A, as taught by Vogl et al and Passey et al, in the kit and method of Hitomi et al, since Hitomi et al teach an ELISA kit and method using antibodies, and calgranulin A can also be detected using antibodies.

Claims 1-31 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

Ilg, Evelyn C. et al. Amino acid sequence determination of human S100A12 (P6, calgranulin c, CGRP, CAAF1) by tandem mass spectrometry. Biochemical and Biophysical Research Communications. 1996, 225:146-150.